Replace the paragraph starting on page 12, line 3 with the following paragraph rewritten in clean form:

In a thirteenth aspect, the invention features a method of making a biomaterial. This method includes (a) attaching a pharmaceutically active compound to a linker molecule or incorporating a nucleophilic amine or thiol into a pharmaceutically active compound, (b) removing any thiol-or amine-protecting groups in the linker, (c) coupling a thiol, amine, or alkene group in the linker or incorporated into the pharmaceutically active compound to a water soluble polymer or a water swellable polymer having two or more conjugated unsaturated groups by a conjugate addition reaction to form a precursor component, and (d) cross-linking the uncoupled conjugated unsaturated groups in one or more of the precursor components. In one preferred embodiment, a polymer that has one or more conjugated unsaturated groups and that is not coupled to a pharmaceutically active moiety is incorporated into the biomaterial by performing the cross-linking in the presence of this polymer. In another preferred embodiment, the cross-linking is performed in the presence of a linker having two or more nucleophilic groups, and the linker is thereby incorporated into the biomaterial. Preferred linkers include a peptide with an amino acid sequence that is 80%, preferably 90%, or more preferably 100% identical to the sequence GCNNRGDNNCG (SEQ ID NO: 75). Other preferred linkers include those having an amino acid sequence or moiety that provides targeting to cells, tissues, organs, organ systems, or sites within a mammal. In one preferred embodiment, the cross-linking step and/or the formation of the precursor components of the

biomaterial occurs within the body of a mammal, such as a human. In another preferred embodiment, the cross-linking occurs through free radical polymerization or conjugate addition reactions at or near a site within the body of a mammal. Preferably, the cross-linking occurs through a self-selective reaction between a thiol or an amine and a conjugated unsaturated group. In another preferred embodiment, the cross-linking forms a hydrogel, a colloidal material, a microsphere, or nanosphere that can be delivered to a mammal, such as a human. In yet another preferred embodiment, the pharmaceutically active compound or a derivative thereof is released from the biomaterial and delivered to a site within the body. Preferably, the half-life the ester or amide bond onto the pharmaceutically active moiety is between 1 hour and 1 year at the site within the body. Preferably, the half-life is between 1 hour and 1 year at pH 7.4 and 37 °C in an aqueous solution. The conjugated unsaturated groups of this aspect may have the same embodiments as listed for the conjugated unsaturated groups of any of the previous aspects.

Replace the paragraph starting on page 46, line 17 with the following paragraph rewritten in clean form:

One can incorporate peptide sites for cell adhesion, namely peptides that bind to adhesion-promoting receptors on the surfaces of cells into the biomaterials of the present invention. It is straightforward to incorporate a variety of such adhesion-promoting peptides, such as the RGD sequence from fibronectin or the YIGSR (SEQ ID NO: 44) sequence from laminin. As above, this can be done, for example, simply by mixing a

cysteine-containing peptide with PEG diacrylate or triacrylate, PEG diacrylamide or triacrylamide or PEG diquinone or triquinone a few minutes before mixing with the remainder of the thiol-containing precursor component. During this first step, the adhesion-promoting peptide will become incorporated into one end of the PEG multiply functionalized with a conjugated unsaturation; when the remaining multithiol is added to the system, a cross-linked network will form. Thus, for example, when an adhesion peptide containing one cysteine is mixed with a PEG triacrylate (at, e.g., 0.1 mole of peptide per mole of acrylate end group), and then a protease substrate peptide containing two cysteine residues is added to form the three-dimensional network (at, e.g., equimolar less 0.1 mole peptide per mole of acrylate end group), the resulting material will be highly biomimetic: the combination of incorporated adhesion sites and protease sites permits a cell to establish traction in the material as it degrades a pathway for its migration, exactly as the cell would naturally do in the extracellular matrix *in vivo*. In this case, the adhesion site is pendantly incorporated into the material. One could also incorporate the adhesion site directly in to the backbone of the material. This could be done in more than one way. One way would be to include two or more thiols (e.g., cysteine) in the adhesion peptide or protein. One could alternatively synthesize the adhesion peptide (e.g., using solution phase chemistry) directly onto a polymer, such as PEG, and include at least one thiol (e.g., cysteine) or conjugated unsaturation per chain end.

Replace the table starting on page 72, line 1 with the following table rewritten in clean form:

Table 1. Plasmin Substrate Sites found in Fibrin (ogen) (Fg)**

Arginyl Sites								
P3	P2	P1	P1'	P2'	P3'	Fg chain and site	Reference	SEQ ID NO:
G	P	R+	V*	V*	E-	α 19	3	8
N	N	R+	D-	N	T	α 104	2, 4	9
Y	N	R+	V*	S	E-	α_110	2	10
Q	M*	R+	M*	E-	L*	α 239	1	11
G	F*	R+	H+	R+	H+	α 491	5	12
G	Y	R+	A*	R+	P	β 42	2, 3	13
Lysyl Sites								
Y	Q	K+	N	N	K+	α_78	3	14
L*	I*	K+	M*	K+	P	α 206	1, 2	15
N	F*	K+	S	Q	L*	α_219	1	16
E-	W	K+	A*	L*	T	α_230	1	17
S	Y	K+	M*	A*	D	α_583	5	18
T	Q	K+	K+	V*	E-	β_53	3	19
R+	Q	K+	Q	V*	K+	β_130	2	20
Q	V*	K+	D-	N	E-	β_133	4	21
L*	I*	K+	A*	I*	Q	γ_62	4	22
T	L*	K+	S	R+	K+	γ_85	2, 3	23
S	R+	K+	M*	L*	E-	γ_88	2	24

Ref. 1: Takagi T. and R.F. Doolittle, Biochemistry 14: 5149-5156 ,1975; Ref. 2: Hantgan R.R., et al., Hemostasis and Thrombosis: Basic Principles and Clinical Practice, Third Edition. Edited by R.W. Colman et al. J.B. Lippincott Company: Philadelphia, 1994; Ref. 3: Takagi T. and R.F. Doolittle, supra.; Ref. 4: Nomura S. et al., Electrophoresis 14: 1318-1321 1993.; Ref. 5: Ständker L. et al., Biochemical and Biophysical Research Communications 215: 896-902 (1995).

* Indicates a hydrophobic amino acid; +/- Indicates a charged side chain, either cationic (+) or anionic (-).

** Single letter amino acid code: A, alanine; C, cysteine; D, aspartic acid; E, glutamic acid; F, phenylalanine; G, glycine; H, histidine; I, isoleucine; K, lysine; M, methionine; N, asparagine; P, proline; Q, glutamine; R, arginine; S, serine; T, threonine; V, valine; W, tryptophan; Y, tyrosine.

Replace the table starting on page 73, line 4 with the following table rewritten in clean form:

Table 2. Collagenase Substrate Sites found in Collagen

P3	P2	P1	P1'	P2'	P3'	Collagen type and site	Ref.	SEQ ID NO:
P	Q	G	I*	A*	G	calf & chick α1(I); human cartilage α 1 (II)	6	25
P	Q	G	L*	L*	G	calf α 2 (I)	6	26
P	Q	G	I*	L*	G	chick α 2 (I)	6	27
P	Q	G	L*	A*	G	chick α 2 (I); human skin α 1 (III)	6	28
P	L*	G	I*	A*	G	human liver α 1 (III)	6	29
P	L*	G	L*	W	A*	human	7	30
P	L*	G	L*	A*	G	human	8	31

Ref. 6: Netzel-Arnett S. et al., The Journal of Biological Chemistry 266: 6747-6755 ,1991; Ref. 7: Upadhye S. and V.S. Ananthanarayanan, Biochemical and Biophysical Research Communications 215: 474-482 ,1995; Ref. 8: Liko Z., et al., Biochem Biophys Res Commun 227: 351-35 , 1996.

Replace the table starting on page 74, line 1 with the following table rewritten in clean form:

Table 3. Design of Collagenase (Matrix metalloproteinase I)-Sensitive Peptide Sequences

No.	Sequence	k_{cat}/ K_m relative to that of PQGIAG	SEQ ID NO:
1	GPQGIAGQ	100% (normal)	32
2	GPVGIAGQ	30% (slow)	33
3	GPQGVAGQ	9% (slower)	34
4	GPQGRAGQ	<5% (very slow)	35
5	GPQGIASQ	130% (fast)	36
6	GPQGIFGQ	>300% (faster)	37
7	GPQGIWGQ	>700% (very fast)	38

Netzel-Arnett S. et al., The Journal of Biological Chemistry 266: 6747-6755 ,1991

Replace the table starting on page 81, line 1 with the following table rewritten in clean form:

Table 4. Cell Binding Domain Sequences of Extracellular Matrix Proteins

Protein	Sequence	Role	SEQ ID NO:
Fibronectin	RGDS	Adhesion of most cells, via $\alpha_5\beta_1$	39
	LDV	Adhesion	N/A
	REDV	Adhesion	40
Vitronectin	RGDV	Adhesion of most cells, via $\alpha_v\beta_3$	41
Laminin A	LRGDN	Adhesion	42
	IKVAV	Neurite extension	43
Laminin B1	YIGSR	Adhesion of many cells, via 67 kD laminin receptor	44
	PDSGR	Adhesion	45
Laminin B2	RNIAEIIKDA	Neurite extension	46
Collagen I	RGDT	Adhesion of most cells	47
	DGEA	Adhesion of platelets, other cells	48
Thrombospondin	RGD	Adhesion of most cells	N/A
	VTXG	Adhesion of platelets	49

After Yamada, Y., and Kleinman, H.K., Curr. Opin. Cell Biol. 4:819, 1992.

Replace the table starting on page 82, line 1 with the following table rewritten in clean form:

Table 5. Proteoglycan Binding Domain Sequences of Extracellular Matrix Proteins

Protein	Sequence	SEQ ID NO:
χBBχBχ*	Consensus sequence	50
PRRARV	fibronectin	51
YEKPGSPPREVVPRPRPGV	fibronectin	52
RPSLAKKQRFRHRNRKGYRSQRGHSRGR	vitronectin	53
RIQNLLKITNLRIKFVK	laminin	54
K(βA)FAKLAARLYRKA	antithrombin III	55
KHKGRDVILKKDVR	neural cell adhesion molecule	56
YKKIIKKL	platelet factor 4	57

References for first five entries given in Massia, S.P., and Hubbell, J.A. J. Biol. Chem. 267:10133-10141, 1992; Antithrombin III sequence from Tyler-Cross, R., et al., Protein Sci. 3: 620-627, 1994; Neural cell adhesion molecule sequence from Kallapur, S.G., and Akeson, R.A., J. Neurosci. Res. 33: 538-548, 1992; Platelet factor 4 sequence from Zucker, M.B., and Katz, I.R., Proc. Soc. Exp. Biol. Med. 198, 693-702, 1991.
*χ indicates a hydrophobic amino acid. Basic amino acids are shown underlined.

Replace the paragraph starting on page 94, line 5 with the following paragraph rewritten in clean form:

The subsequent cross-linking reaction can generally occur by two main routes, utilizing either free-radical polymerization (Lau *et al.*, *Bioorg. Med. Chem.* 3:1305-1312, 1995) or conjugate addition reactions. The conjugated unsaturated groups of the present invention that are reacted with good nucleophiles via conjugate addition reactions can generally also be polymerized by free-radical mechanisms. Thus, as long at least one conjugated unsaturated group remains on the polymer following the coupling of the pharmaceutically active compound, then that polymer can be incorporated into a biomaterial by free-radical mechanisms. The presence of at least one unreacted

unsaturated group on the polymer is assured by keeping the number of unsaturated groups in excess compared to the thiol or amine groups present in, or coupled to, the pharmaceutically active moiety. The second route to cross-link these materials involves reacting the remaining conjugated unsaturated groups on the polymer coupled to a pharmaceutically active moiety with cross-linker molecules containing 2 or more nucleophiles, such as the peptide GCNNRGDNNCG (SEQ ID NO: 75) that increases cell adhesion to basement membranes. The cross-linking to form a material then occurs through another conjugate addition reaction.

Replace the paragraph starting on page 102, line 4 with the following paragraph rewritten in clean form:

Gels were formed from PEG-2500-3A and GCYKNRDCG (SEQ ID NO: 58) as well as from PEG-3500-3A and GCYKNRDCG (SEQ ID NO: 58). Gels have been formed at three ratios of acrylates to sulfhydryls (1: 1, 1.1: 1, and 1.25: 1). Gels were formed in 10 mM phosphate buffered saline with triethanolamine to adjust the pH to 8.0-9.0 as tested by paper pH strips (gel formation reactions were performed at 50 microliter and smaller scales). Gels have been made by: predissolving the peptide and then adding peptide solution to PEG-3A; by predissolving the PEG-3A and adding its solution to the peptide; and by predissolving both solutions and then mixing them in appropriate ratios.

Replace the paragraph starting on page 102, line 18 with the following paragraph rewritten in clean form:

2.5 mg of GCYKNRDCG (SEQ ID NO: 58) were weighed into an Eppendorf tube. 7.0 mg of PEG-2500-3A were weighed into a separate Eppendorf tube. 62 microliters of phosphate buffered saline (PBS)•TEA (10 mM PBS with 13 microliters of triethanolamine/ml) were added to the PEG-2500-3A to give a solution of 4.5 mg/40 microliters. The PEG solution was allowed to sit until the PEG-3A had dissolved (less than five minutes). 40 microliters of the PEG-3A solution were added to the peptide, which dissolved extremely rapidly. The pipet tip used for the transfer was used to stir the mixture for approximately 3 seconds. A 1 microliter sample was withdrawn to test the pH by a paper strip (pH range 1-11). The pH was approximately 8.0. After 20-30 minutes, a gel had formed.

Replace the paragraph starting on page 103, line 22 with the following paragraph rewritten in clean form:

Gels were made with 0.1 g/ml, 0.15 g/ml, and 0.2 g/ml PEG-2500-3A at a 20 microliter scale. The gels contained 1.1 acrylates per sulfhydryl in the peptide (nucleophile) component, GCYKNRDCG (SEQ ID NO: 58). For gel formation, PBS buffers were adjusted to account for added acidity of additional peptide in higher concentration gels and to give reactions at pH 8.0-8.5. Gels were made in quadruplicate.

Replace the paragraph starting on page 106, line 3 with the following paragraph rewritten in clean form:

13.9 mg PEG-2500-3A was dissolved in 69.5 microliters (5.0 mg/25 microliters) of PBS•TEA (10 mM PBS containing 13 microliters of triethanolamine/ml) containing GCGYGRGDSPG (SEQ ID NO: 61) at a concentration of 3.2 mg GCGYGRGDSPG (SEQ ID NO: 61)/ml. 7.0 mg GCYKNRDCG (SEQ ID NO: 58) was dissolved in 65 microliters of PBS•TEA (2.7 mg/25 microliter). The GCYKNRDCG (SEQ ID NO: 58) was filtered through a 0.22 micron filter. After 9 minutes of reaction time, the PEG-2500-3A/GCGYGRGDSPG (SEQ ID NO: 61) solution was separately filtered through a 0.22 micron filter. As soon as the filtrations were complete, equivolumes (25 microliters) of the two solutions were added to wells of a Corning flat-bottomed tissue culture treated polystyrene 96 well plates. As the second of the two precursor solutions was added, the pipet tip was used to stir the mixture for 2-3 seconds. Then the gels were allowed to set at 37°C.

Replace the paragraph starting on page 106, line 18 with the following paragraph rewritten in clean form:

Conjugate addition gels were made with 0.1 g/ml PEG-2500-3A and 1.1 acrylates per sulfhydryl in GCYKNRDCG (SEQ ID NO: 58). The gels were swollen for 24 hours in Dulbecco's modified Eagle's medium (some in serum-free conditions and some in 10% fetal bovine serum) containing 1% antibiotic and antimycotic agents. Human foreskin fibroblasts (passage 7; passaged with trypsin/EDTA) were seeded onto the gels. From time points two hours to 48 hours, the cells remained round and did not spread. The cells became increasingly clumped together. The cellular behavior was independent of serum

in the medium. Control cells seeded on tissue culture treated polystyrene spread normally.

Replace the paragraph starting on page 107, line 5 with the following paragraph rewritten in clean form:

Conjugate addition gels were made with PEG-2500-3A, GCYKNRDCG (SEQ ID NO: 58), and an RGD-containing peptide (GCGYGRGDSPG (SEQ ID NO: 61)) incorporated in a pendant fashion. The gels were made with 0.1 g PEG-2500-3A/ml and 1.1 acrylates per sulfhydryl in GCYKNRDCG (SEQ ID NO: 58). The gels were swollen for more than 36 hours in Dulbecco's modified Eagle's medium (some in serum-free conditions and some in 10% fetal bovine serum) containing 1% antibiotic and antimycotic agents. When the RGD peptide was incorporated on one of every 12 acrylates of the PEG-2500-3A, human foreskin fibroblasts (passage 8; passaged by trypsin/EDTA) adhered to the gels (both those swollen in serum-free conditions and those in serum-containing medium). At 6 hours post-seeding, the cells were uniformly distributed over the gel surface, and approximately 50% of the seeded cells were spread (in both medium conditions).

Replace the paragraph starting on page 111, line 3 with the following paragraph rewritten in clean form:

Aqueous size exclusion chromatography was performed using a Shodex OHpak SB-803 column (Showa Denko, Tokyo, Japan), using UV detection, measuring

absorbance from 200-400 nm. The eluent was phosphate buffered saline (10 mM sodium phosphate, 140 mM NaCl, pH 7.4). PEG diacrylate has maximum absorbance at 205 nm, whereas the peptide used, GCGYGRGDS (SEQ ID NO: 64) has absorbance maxima at 220 and 270 nm, due to the presence of amide bonds, and a tyrosine. PEG diacrylate was dissolved in 0.1 M phosphate buffer at pH 8 at a concentration of 25 μmol in 1 ml. A sample of the solution was separated using size exclusion chromatography, and the polyethylene glycol eluted as a single peak with an absorbance maximum at 205 nm, and no absorbance at 220 or 270 nm. Next, the peptide (12.5 μmol) was added to the PEG diacrylate solution, and reacted at room temperature for 5 min. A sample was then separated using size exclusion chromatography, and a single peak was detected, with absorbance maxima at 205, 220, and 270 nm, with the same retention time as PEG diacrylate. This indicated that the peptide reacted with the PEG diacrylate. Similar studies were performed using C18 chromatography, using a gradient from 95% water with 0.1% trifluoroacetic acid, 5% acetonitrile to 40% water with 0.1% trifluoroacetic acid, 60% acetonitrile. The peptide Ac-GCGYGRGDSP-NH_2 (SEQ ID NO: 62), eluted at about 20% acteonitrile, whereas PEG or PEG-3400 diacrylate eluted at about 40% acetonitrile. Incubation of 1 mol of the peptide per 2 mol of PEG-3400 diacrylate in buffered water at pH 8 led to the disappearance of the peptide-related peak that elutes at 20% acetonitrile, with the emergence of absorbance bands at 220 and 270 nm that coeluted with the PEG peak at 40% acetonitrile. Collecting the peaks and analyzing by MALDI-TOF mass spectrometry indicated that the PEG-associated peak contained a

mixture of unmodified PEG-3400 diacrylate, and a new species with molecular weight that was the sum of the PEG-3400 diacrylate and the peptide molecular weights.

Replace the paragraph starting on page 113, line 1 with the following paragraph rewritten in clean form:

The peptide Ac-GCGYGRGDSP-NH_2 (SEQ ID NO: 62) was dissolved in deionized water, and PEG-8000 diacrylate was dissolved in deionized water buffered with 10 mM HEPES and 115 mM triethanolamine at pH 8. After mixing 1 mol of the peptide per 2 mol of the PEG-8000 diacrylate, the reaction was followed by C18 chromatography, using a gradient from 95% water with 0.1% trifluoroacetic acid, 5% acetonitrile to 40% water with 0.1% trifluoroacetic acid, 60% acetonitrile. The peptide Ac-GCGYGRGDSP-NH_2 (SEQ ID NO: 62), eluted at about 20% acteonitrile, whereas PEG or PEG-8000 diacrylate eluted at about 40% acetonitrile. Rapidly, the free peptide peak at 20% acetonitrile disappeared, and the peptide then coeluted with the PEG peak at 40% acetonitrile. The solution containing the PEG-peptide adduct was then incubated at 37°C, and C18 chromatographic injections were made at later time points to detect hydrolysis of the peptide from the polymer. This was measured by observing the decrease in signal at 273 nm that coeluted with the PEG peak, and the reappearance of the free peptide peak at about 20% acetonitrile. MALDI-TOF mass spectrometry of the new peak eluting at about 20% acetonitrile revealed a product of molecular weight which corresponded to the molecular weight of the original peptide plus 72 mass units. This indicated that the new peak contains peptide modified with propionic acid, which was the

product that would be expected following conjugate addition between the cysteine on the peptide and an acrylate group, followed by hydrolysis of the ester of the modified acrylate. A half-life for hydrolysis of the ester between the peptide and the PEG was found to be 4.86 days. This corresponds to a half-life of hydrolysis of about 3 weeks at pH 7.4.

Replace the paragraph starting on page 114, line 16 with the following paragraph rewritten in clean form:

13.9 mg PEG-2500-3A was dissolved in 69.5 microliters (5.0 mg/25 microliters) of PBS•TEA (10 mM PBS containing 13 microliters of triethanolamine/ml). 7.0 mg of GCYKNRDCG (SEQ ID NO: 58) was dissolved in 65 microliters of PBS•TEA (2.7 mg/25 microliter). Equivolumes (25 microliters) of the two solutions were added to wells of a Corning flat-bottomed tissue culture treated polystyrene 96 well plates. As the second of the two precursor solutions was added, the pipet tip was used to stir the mixture for 2-3 seconds. Then the gels were allowed to set at 37°C. The gels were then transferred to tubes containing 10 mM HEPES buffered saline, pH 7.4. The gels were incubated at 37°C, and the disappearance of the solid gels was followed visually. Between 14 and 21 days, all of the solid gels were gone, indicating that they had degraded by hydrolysis of the ester bond between the peptide and the PEG.

Replace the paragraph starting on page 115, line 5 with the following paragraph rewritten in clean form:

13.9 mg PEG-2500-3A is dissolved in 69.5 microliters (5.0 mg/25 microliters) of PBS•TEA (10 mM PBS containing 13 microliters of triethanolamine/ml). 7.0 mg of GKKKKGCYKNRDCG (SEQ ID NO: 65) is dissolved in 65 microliters of PBS•TEA (2.7 mg/25 microliter). Equivolumes (25 microliters) of the two solutions are added to wells of a Corning flat-bottomed tissue culture treated polystyrene 96 well plates. As the second of the two precursor solutions is added, the pipet tip is used to stir the mixture for 2-3 seconds. Then the gels are allowed to set at 37°C. The gels are then transferred to tubes containing 10 mM HEPES buffered saline, pH 7.4. The gels are incubated at 37°C, and the disappearance of the solid gels is followed visually. The extra lysines found in the peptide ("GKKKK..." (SEQ ID NO: 73)) are added so as to provide additional nucleophiles to the local environment of the ester bond. Additionally, the cationic nature of the groups may also lead to a raising of the local pH. The combination of these two effects is expected to enhance the rate of hydrolysis of the ester bond between the peptide and the polymer.

Replace the paragraph starting on page 115, line 25 with the following paragraph rewritten in clean form:

Since enzymes and peptides are chiral, the stereochemistry of GCYKNRDCG (SEQ ID NO: 58) was altered to make a plasmin-stable nucleophile for gels made by conjugate addition. This plasmin stable peptide was: GCY-DLys-N-DArg-DCG (SEQ ID NO: 66). The sequence was otherwise not altered in order to maintain the extremely good water solubility properties of GCYKNRDCG (SEQ ID NO: 58).

Replace the paragraph starting on page 116, line 5 with the following paragraph rewritten in clean form:

Analytical C18 HPLC (linear acetonitrile gradient over 0.1% TFA in water) was used to confirm the relative plasmin-stability of GCY-DLys-N-DArg-DCG (SEQ ID NO: 66). The following samples were run: plasmin; GCYKNRDCG (SEQ ID NO: 58); plasmin + GCYKNRDCG (SEQ ID NO: 58); GCY-DLys-N-DArg-DCG (SEQ ID NO: 66); and plasmin + GCY-DLys-N-DArg-DCG (SEQ ID NO: 66). Plasmin (micromolar) was present at 1/1000 the concentration of the peptide (millimolar) and hence did not affect overlaid absorbance chromatograms. Overlaying the traces (absorbance at 220 nm or 278 nm) of the peptide elutions vs. those of the peptide + plasmin, demonstrated that most of the GCYKNRDCG (SEQ ID NO: 58) peptide was degraded in approximately 1 hour at 37°C. The GCY-DLys-N-DArg-DCG (SEQ ID NO: 66) peptide however, was unaffected by the plasmin at 24 hours, and remained unaffected over the lifetime of the plasmin in the sample (sample injected for C18 at 2 weeks).

Replace the paragraph starting on page 116, line 20 with the following paragraph rewritten in clean form:

Gels were made according to the 40 microliter protocol given above. Some contained the GCYKNRDCG (SEQ ID NO: 58) peptide with Lys and Arg in the L configuration. Another contained the GCY-DLys-N-DArg-DCG (SEQ ID NO: 66) instead. All were exposed to 0.2 units of plasmin in 200 microliters and incubated at

37°C. The L-Lys, L-Arg configuration of the peptide was readily degraded by the enzyme. In one case, after 6 hours no gel remained. The DLys, DArg configuration gel has not been shown to degrade by plasminolysis.

Replace the paragraph starting on page 117, line 19 with the following paragraph rewritten in clean form:

PEG gels were prepared as described above, using the peptide GCGYGRGDSPG (SEQ ID NO: 61). Most cells have receptors that recognize the sequence GRGDSPG (SEQ ID NO: 74), and cells will interact with surfaces displaying immobilized RGD containing peptides. To test cellular interactions of cells with PEG gels containing peptides incorporated via conjugate addition, gels were formed and human umbilical vein endothelial cells were seeded onto the gels. The change in the shape of the cells on the surface was observed, which indicated that the cells were interacting with the peptides on the surface. The change in shape is referred to as spreading, and refers to the change of the cell shape from spherical to flattened and polygonal on the surface. No cell spreading occurred on the PEG gels without peptide, and the specificity of the GCGYGRGDSPG (SEQ ID NO: 61) peptide was confirmed by comparison with gels containing the peptide GCGYGRDGSPG (SEQ ID NO: 68), which contains the same amino acids, but in a different sequence, and which has no biological activity. Cells were seeded onto the gels at a concentration of 400 cells per mm^2, and the number of spread cells per area was counted at different times (see Figure 6). The experiments were performed using the normal cell culture medium. Cells could only spread on gels that contained the peptide

GCGYGRGDSPG (SEQ ID NO: 61), which was incorporated into the gels utilizing a conjugate addition reaction.

Replace the paragraph starting on page 119, line 20 with the following paragraph rewritten in clean form:

Microspheres are formed via conjugate addition cross-linking of PEG-triacrylate and the peptide GCYdKNdRDCG (SEQ ID NO: 66) as in Example 7, but additionally the peptide GCGYGRGDSPG (SEQ ID NO: 61) is also included in the reaction mixture, at a ratio of 1 GCGYGRGDSPG (SEQ ID NO: 61) to 8 GCYdKNdRDCG (SEQ ID NO: 66). The bioactive peptide is tested for the ability to localize microspheres to the surfaces of cells, as compared with microspheres containing no bioactive peptide.

Replace the paragraph starting on page 120, line 22 with the following paragraph rewritten in clean form:

The protein myoglobin (17,000 Da) was released from hydrogels made by conjugate addition between thiols and acrylates. PEG-3500-3A at 0.2 g/ml in PBS, pH 7.4 was mixed with a solution of the plasmin sensitive peptide GCYKNRDCG (SEQ ID NO: 58) such that the concentration of thiols and acrylates was the same and the final concentration of PEG-3500-3A was 10% (precursor solution). To some of the precursor solution, myoglobin was added (5.2 µl of 9.8 mg/ml myoglobin solution per 195 µl of precursor solution). Myoglobin was chosen as a model protein for growth factors, such as BMP-2, because of its similar size. 200 µl aliquots of precursor solution with and

without myoglobin were made onto hemostatic collagen sponges. To some control sponges 5.2 µl of the 9.8 mg/ml myoglobin solution were added without gel precursors. To some sponges, PBS was added instead of myoglobin. After gels had solidified within the sponges, each sample was incubated in 4 ml of 10 mM PBS, pH 7.4, containing 0.1% sodium azide to prevent bacterial and fungal contamination. At 6 hr, 12 hr, 24 hr, 2 d, 3 d, 7 d, and 13 d the solution phase was removed from each sample and replaced with fresh PBS with 0.1% sodium azide. After day 13, the solutions were replaced with 0.08 units of plasmin in 4 ml PBS, the discontinuity marked by the vertical line in Figure 7. Solutions were developed using the BIORAD/Bradford protein microassay and compared to a standard curve made from myoglobin solutions of known concentration. The samples with myoglobin within the hydrogel material showed a delayed release of the myoglobin (diffusion limited) but did, following hydrogel degradation by the enzyme plasmin, release a total amount of protein not different from the total released from the sponges alone (no hydrogel) (data not shown).

Replace the paragraph starting on page 125, line 3 with the following paragraph rewritten in clean form:

For example, the DNA for vascular endothelial growth factor (VEGF) is modified using site directed mutagenesis to introduce a cysteine near the N terminus of the protein. Molecular biological techniques are used to synthesize, purify and fold the protein. The protein is incubated with PEG-triacrylate with acrylates in excess of thiols in the protein.

A plasmin sensitive peptide containing two thiols (GCYKNRDCG (SEQ ID NO: 58)) is added to cross-link the material with the growth factor incorporated throughout.

Replace the paragraph starting on page 127, line 9 with the following paragraph rewritten in clean form:

Materials were made essentially according to Example 3, but under sterile conditions and with PEG-3500-3A, a molar ratio of acrylates: thiols of 1:1, and a molar ratio of GCGYGRGDSPG (SEQ ID NO: 61): acrylates of 1/12. At the time of gel formation, a recombinant human growth factor, BMP-2, which induces bone formation was added to the precursor solution at a concentration of 250 μg/ml of precursor solution. Precursor solution was added to hemostatic collagen sponges (Helistat; 8 mm diameter, approximately 3.5 mm height). Precursor solution was added until the sponges could not absorb more solution (approximately 160 μl). The gels were allowed to solidify in the sponges. Gels were briefly washed with PBS then kept minimally wet until implantation subcutaneously in rats. The implants were removed after two weeks, fixed, and hematoxylin and eosin stained. The materials were well infiltrated by cells with very little residual material remaining and promoted bone formation (mineralization and marrow formation) and vascularization. This indicates that the materials can deliver active biomolecules (e.g., growth factors) and can be infiltrated by cells *in vivo*.

Please insert the enclosed Sequence Listing after the Abstract of the Disclosure.